Improving IL-15 antitumor efficacy:
fusion protein strategy

- **Apolipoprotein A-I (Apo-AI)** is the major protein constituent of the HDL particles.
- **Apo-AI fusion proteins** have an optimized pharmacokinetic/pharmacodynamic profile as they show the following properties:
  - Apo-AI increases the plasmatic **half-life** and the **liver** retention of the fused proteins.
  - **Blood-brain barrier active transport**, mediated by a saturable transporter that limits the amount of the fusion protein in the central nervous system.
  - **Modulation of activity**: Apo-AI activates MAPKs through ABCA1 and SR-BI and, therefore, modulates the therapeutic effect of fused proteins.
- **Sushi-IL-15-Apo** is a new **proprietary triple fusion protein** developed combining apolipoprotein A-I, IL-15 and IL-15Rα's sushi, with:
  - Superior antitumor effect than IL-15 as a single agent.
  - Higher capacity than hIL15 to enhance antibody dependent cell cytotoxicity (ADCC) when combined with monoclonal antibodies.
  - Increased stability in circulation.
  - Facilitated trans-presentation.
- **Primary Indication**: adjuvant of tumor specific antigen antibodies in lymphoma, breast cancer and colorectal cancer treatment.

Medical need	Enhancement of the immune response against the tumors with emphasis in **synergistic approaches** with the current standard of care.
Proof of Concept	· Immunotherapeutic effects against metastatic disease in *in vivo* tumor models, (B16OVA lung metastasis of melanoma & MC38 colon cancer liver metastasis). · *In vitro* assays testing the ADCC capacity of Sushi-IL15-Apo in combination with cetuximab against colorectal cancer-derived cell lines.
Safety	· Toxicity is an on-target side effect; a therapeutic window has been found. · Repeated doses are feasible without desensitization or cumulative toxicity.

Product Profile

- A plasmid encoding a triple fusion protein combining apolipoprotein A-I, IL-15 and the Sushi domain.
- Apo A-I acts as a natural vehicle that facilitates the IL-15/IL-15Ra sushi domain anchorage for trans-presentation of the cytokine.
- pSushi-IL-15-Apo is highly active and plasmid doses within the therapeutic range have been identified.
- These plasmid doses were tolerated and promoted the proliferation and accumulation of NK and memory CD8+ T cell in the spleen and in the liver (Fig. 1 and Fig. 2).
- In a classical cromium release assays it has been shown that human Sushi-IL15-Apo protein increases ADCC capacity of cetuximab against a tumoral cell line (Fig. 3).

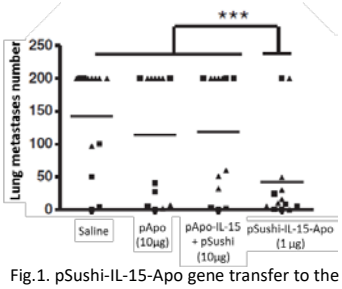

Fig.1. pSushi-IL-15-Apo gene transfer to the liver ameliorates melanoma lung metastasis of B16OVA.

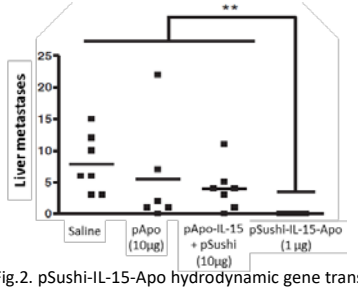

Fig.2. pSushi-IL-15-Apo hydrodynamic gene transfer is active against liver metastases of MC38 colon carcinoma.

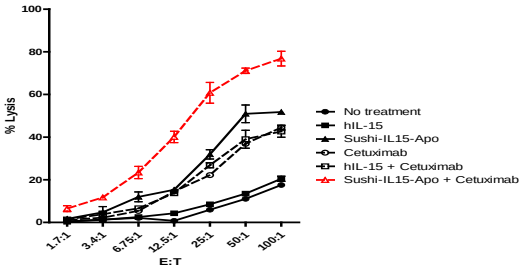

Fig.3. Human Sushi-IL-15-Apo increases ADCC capacity of cetuximab in chromium^{51} release assays against HT-29 colon-carcinoma cells.

Apo Platform: other fusion proteins	· InterApo: ApoA-I fused to IFNα. · Apo-Linker-144: Apo-AI fused to P144, an inhibitor peptide of TGFβ. · Apo-CT1: Apo-AI fused to cardiotrophin 1. · Other fusion proteins are under development.
Intellectual Property	WO2009150284. Conjugates for the administration of biologically active compounds. WO2011070214. Novel conjugates and compositions for immunotherapy and antineoplastic treatment. Patent issued in US, EP, JP, AU, CN, MX, RU; Pending in BR, CA, IN.

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